petition for a three-month extension of time, and the appropriate fee, accompany this response.

Claims 1-21, 23, and 25 were pending. All pending claims were rejected in the Office Action.

Claims 1, 11, 12, 14, 15, and 23 have been amended herein. Claim 2 has been cancelled without prejudice. In view of the foregoing amendments and arguments that follow, Applicants respectfully request withdrawal of all rejections upon reconsideration.

Preliminarily, Applicants note the requirement for new drawings. New drawings are being forwarded under separate cover to the draftsman.

Applicants also observe that several interview summaries purportedly summarizing the substance of interviews occurring on May 23, 2001, June 5, 2001, and July 13, 2001 between the Examiner and the undersigned are attached to the Office Action. The undersigned is somewhat concerned that these summaries were not forwarded earlier. The undesigned requests that the Examiner advise whether the summaries were prepared contemporaneously with the actual interviews. If they were not, then their accuracy must surely be questioned as the interviews were conducted not less than **two**, and in one instance more than **four**, months earlier. If the interview summaries were prepared contemporaneously with the interviews, then the undersigned must question why they were not forwarded earlier.

Nonetheless, the interview summaries help document the extreme protraction of prosecution of this application. This is the **fourth** office action. Yet, Applicants must argue over **new** rejections of claim language that was present in the claims as **originally filed** and over **new** art that is just as lacking as art previous cited. Such piecemeal examination is inappropriate. See MPEP 707.07(g).

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-21, 23, and 25 were rejected as allegedly indefinite in view of the recitation "episomal." Focusing upon the definition for "episome," not episomal, the Examiner argued that an episome can replicate autonomously or in the chromosome of the host cell and that, therefore, the claims read on vectors that integrate into the chromosome (Office Action, pages 2-3). (The Examiner said "vectors that do not integrate into the chromosome", but it is assumed she meant to say that they do integrate. See Office Action, page 3.) The problem

appears to be that the Examiner is focusing upon the noun instead of the adjective and presuming the adjective is defined similarly as the noun. The two, however, are not defined similarly by the art. Applicants submit the enclosed definition of "episomal" from a 1988 dictionary of biotechnology:

> **Episomal:** Existing as an independent, autonomously replicating, genetic element not associated with cellular chromosomes.

The Language of Biotechnology, A Dictionary of Terms, p. 89, J.M. Walker and M. Cox, American Chemical Society, Washington, D.C., 1988, emphasis in the original (copy enclosed). On that same page, the noun "episomes" is defined as "plasmids that replicate by inserting themselves into the bacterial chromosome. . .but at some stage exist as independent elements." *Id.* Thus, when the **adjective** "episomal" is used, it is interpreted by the art as Applicants have used it, i.e., to mean extrachromosomal. Nonetheless, to advance prosecution, Applicants have amended the claims to recite that the expression occurs "extrachromosomally." Support for this amendment can be found, for example, on page 12, lines 2-3, of the application as filed wherein it is stated that the episomal DNA replicates "independent of the host cell chromosomes. . ." Applicants respectfully request that this rejection be withdrawn.

Claims 1 and 6-11 were rejected as allegedly indefinite in view of the recitation "for expressing a gene of interest in a host cell" because the claims do not include a gene of interest as a structural element. Applicants have amended claim 1 to recite "a cloning site for a gene of interest." Support for this amendment can be found, for example, in claim 12 as originally filed. Applicants respectfully request that this rejection be withdrawn.

Claims 3 and 5 were rejected as allegedly indefinite in view of the recitation "the component of an LCR" as allegedly lacking antecedent basis. Claim 1, however, recites "an LCR, **or component thereof**" (emphasis added). This rejection is inappropriate and should be withdrawn.

Claims 3 and 5 were also rejected as allegedly indefinite "because it is unclear if Claims 3 and 5 are intended to be limited to the specific components recited therein or not." (See Office Action, page 3.) Applicants respectfully traverse.

Claims 3 and 5 ultimately depend from claim 1 which recites "an LCR, **or**

component thereof" (emphasis added). Clearly, then, if claims 3 and 5 are reciting a specific component, they are not covering the entire LCR. If the Examiner prefers, however, Applicants will amend claims 3 and 5 to recite "wherein said vector comprises a component of an LCR . . .", before the phrase "wherein the component of an LCR is . . ." but feel such an amendment is unnecessary.

Claim 14 was rejected as allegedly indefinite in view of some missing language that was not entered from an amendment filed July 14, 2000. That amendment is duplicated herein. This rejection should be withdrawn.

Claim 15 was rejected as allegedly indefinite in view of the recitation "wherein the LCR, or component thereof is the β-globin LCR or component thereof excluding site HS2." Claim 15 has been amended to clarify that the claim is reciting a component which comprises the β-globin LCR **minus** site HS2. Applicants request that this rejection be withdrawn.

Claim 23 was rejected as allegedly indefinite for omitting the element "a gene of interest." Claim 23, as amended herein, refers to claims 2 and 13. Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Claims 1 and 2 were rejected as allegedly anticipated by Safaya et al. (1994) ("Safaya"). To anticipate, each and every element as set forth in the claims must be found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants traverse this rejection.

The Examiner alleges that the composition of Safaya "has all the structural elements recited in the claims." (See Office Action, page 5.) The Examiner bases this allegation upon the assertion that the specification does not limit the origin of replication to any particular type of origin of replication. The Examiner is not correct. The claims recite that the vector has a "self-replicating origin of replication." The claims further recite that the vector is to replicate in a "host cell of a specific **tissue** type." The latter recitation is a functional limitation. The Examiner is reminded that there is nothing inherently wrong with defining a part of an invention in functional terms. MPEP 2173.05(g). Functional limitations that set definite boundaries in the patent protection sought are "perfectly acceptable." *Id.* The recitation that the vector replicate in

a "host cell of a specific tissue type" is such a limitation. The Examiner continues to mischaracterize this phrase as an intended use rather than a functional limitation and, thus, disregards it. But even an intended use cannot be disregarded if it results in structural differences between the claimed invention and the prior art. MPEP 2111.02, page 2100-38.

As discussed with the Examiner and her Supervisory Patent Examiner in one of the interviews noted above, and as referenced in the Office Action, the origin of replication used in Safaya facilitates replication only in bacteria (see page 7 of the Office Action). Tissue is not made up of bacteria. Thus, origins of replication that function only in bacteria do not satisfy the functional limitation. Accordingly, Safaya does not disclose each and every element of claims 1 and 2 as set forth in those claims.

To further clarify, Applicants have amended the claims to recite that the self-replicating origin of replication is "operative in mammalian host cells." Support for this amendment can be found, for example, on page 37, lines 4-14 of the application as filed, wherein delivery of the vectors according to the invention to mammals both *in vivo* and *ex vivo* is discussed.

Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Claims 1, 2, and 10 were rejected as allegedly anticipated by U.S. Patent No. 6,022,738, filed March 3, 1995, issued February 8, 2000 ("Atweh"). To anticipate, each and every element as set forth in the claims must be found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully traverse this rejection.

The Examiner alleges that the composition of Atweh has all the structural elements recited in the claims. Applicants disagree. As discussed above, discussion incorporated herein, the adjective "episomal" means extrachromosomal. There is no evidence that the vectors described in Atweh function extrachromosomally. Indeed, the evidence is to the contrary.

The problem being solved in Atweh was the instability of viral sequences having the β-LCR element **after integration** into host cells because they were so **"recombinogenic"**

(see Atweh, col. 2, lines 40-45). Accordingly, the α-LCR element was used instead of β-LCR. Atweh states that the stability of integration of vectors using α-LCR was tested by isolating **genomic** DNA cut with a restriction enzyme, or by **PCR amplification** (see Atweh, col. 6, lines 51-65). These vectors, thus, were clearly not extrachromosomal. Accordingly, Atweh does not disclose each and every element of claims 1, 2, and 10 as set forth in those claims.

Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.

MPEP, 2143 citation omitted. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for all claim rejections discussed below.

Claims 6, 8, 9, 11, 12, 13, 17, and 19-21 were rejected as allegedly obvious over Atweh in view of U.S. Patent No. 5,674,703 ("Woo"). Applicants traverse this rejection.

The Examiner alleges that Woo discloses using episomal vectors for tissue-specific expression (see Office Action, page 10). The Examiner fails to acknowledge, however, that Woo suggests using tissue-specific **promoters** to achieve that end, not **LCRs**. Further, Woo describes using episomal, i.e., extrachromosomal, vectors while Atweh describes using **integrating** vectors. Thus, even if combined, the references do not yield Applicants' invention.

It is only by picking and choosing elements from the references that the Examiner can hope to yield Applicants' invention. Such picking and choosing can only be accomplished,

however, using the Applicants' disclosure as a template. The Federal Circuit recently reiterated the prohibition against the use of a patent specification as a template for piecing together teachings from multiple references in support of an obviousness rejection, stating that "[i]t is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to 'use that which the inventor taught against its teacher.'" *In re Lee*, 61 U.S.P.Q.2d 1430, 1434 (Fed. Cir. 2002). (citing *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)).

Indeed, the Examiner's arguments for motivation are flawed. For example, one argument set forth by the Examiner is the desirability of achieving stable gene transfer and the of use of the known LCR sequences to achieve the same (see Office Action, page 11). But, the Examiner is clearly disregarding the teachings of Woo to maintain this argument. Woo defines **episomal** transformation as "**stable** transformation" (Woo, col. 7, lines 18-23). Thus, there is no motivation to combine Woo with Atweh to achieve stability.

Applicants acknowledge that the art separately describes 1) using LCRs in integrating vectors and 2) using episomal vectors. Applicants maintain, however, that the art did not disclose or suggest the combination of LCRs with episomal vectors, nor was there motivation to do so. As stated in the enclosed Declaration of Dr. Michael Antoniou ("Declaration"), one of the co-inventors of the present application, there was simply no motivation to combine the concepts, much less the two references. (See Declaration, ¶ 3.) As Dr. Antoniou observes, both LCRs and episomal (extrachromosomal) vectors were described in the literature over 15 years ago. Yet, the application from which the present application ultimately claims priority was not filed until 9 years after that. (*Id.*) The dogma at that time was that LCRs would not function in episomal vectors. Indeed, the prevailing opinion in the art, based upon published results at the time, was that the two systems, i.e., LCRs and episomal vectors, were incompatible. (*Id.*) Indeed, when Applicants performed their initial experiments, their expectation was that the LCRs would not function in the episomal vectors. (*Id.*) The Examiner is clearly using inappropriate hindsight reconstruction to maintain this rejection.

Applicants request that this rejection be withdrawn.

Claims 7, 9, 18, and 19 were rejected as allegedly obvious over Atweh and Woo,

as applied to claims 6, 8, 9, 11,12,13,17, and 19-21, further in view of Yates et al. (1985) ("Yates"). Applicants traverse this rejection.

As set forth above, discussion incorporated herein, there is no motivation to combine Atweh and Woo and, even if combined, the references do not yield Applicants' invention. Yates does not provide the requisite motivation to combine, nor does it overcome the deficiencies of Atweh and Woo. The Examiner relies upon Yates merely for piecing together the additional recitations in claims 7, 9, 18, and 19. This, again, is inappropriate hindsight reconstruction.

Applicants request that this rejection be withdrawn.

Claim 23 was rejected as allegedly obvious over Atweh and Woo as applied to claims 6, 8, 9, 11, 12, 13, 17, and 19-21 further in view of Chapman et al. (1991) ("Chapman"). Applicants respectfully traverse this rejection.

As set forth above, discussion incorporated herein, there is no motivation to combine Atweh and Woo and, even if combined, the references do not yield Applicants' invention. Chapman does not provide the requisite motivation to combine, nor does it overcome the deficiencies of Atweh and Woo. Chapman is merely relied upon for the transfection of cultured cells. The Examiner is relying upon Chapman for inappropriate hindsight reconstruction.

Applicants request that this rejection be withdrawn.

Claim 25 was rejected as allegedly obvious over Atweh as applied to claims 1, 2, and 10, further in view of Chapman. Applicants respectfully traverse this rejection.

The deficiencies of Atweh are discussed above, discussion incorporated herein. Since Atweh does not disclose an episomal vector with an LCR, it cannot possibly suggest a method for identifying an LCR directing expression in a tissue-specific manner when on an episomal vector. Chapman does not overcome this deficiency. Chapman is relied upon for disclosing the effect of intron A from human cytomegalovirus immediate early gene on heterologous expression in mammalian cells. Chapman, however, does not even suggest testing candidate regulatory elements, much less LCRs.

Applicants respectfully request that this rejection be withdrawn.

For the foregoing reasons, the Applicants submit that the present claims are in condition for allowance. Applicants respectfully request early notification of the same. If the Examiner feels further discussion would be helpful, she is asked to call the undersigned at 215-564-8352.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made.**"

Respectfully submitted

Date: March 26, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend the claims as follows:

1. (Twice Amended) A self-replicating episomal DNA expression vector for expressing a gene of interest extrachromosomally in a host cell of a specific tissue type, the vector comprising:

(a) a self-replicating origin of replication operative in mammalian host cells;

(b) an LCR, or component thereof, which when operatively linked to a gene of interest and present in a host cell directs expression of said gene in a tissue-restricted manner; and

(c) a cloning site for a gene of interest.

11. (Amended Once) The self-replicating episomal DNA expression vector of claim 1, further comprising a eukaryotic transcription termination sequence placed between the LCR and the cloning site for a gene of interest and operative to prevent transcription therebetween.

12. (Twice Amended) A pair of vectors comprising a self-replicating episomal expression system for expressing a gene of interest extrachromosomally in a host cell [in a tissue-restricted manner] of a specific tissue type, the pair of vectors comprising:

i. a first vector comprising

(a) [an] a self-replicating origin of replication operative in mammalian host cells;

(b) an LCR, or component thereof, which when operatively linked to a gene of

interest and present in a host cell directs expression of said gene in a tissue-restricted manner; and

(c) a cloning site for a gene of interest; and

ii. a second vector comprising

(a) said origin of replication; and

(b) a sequence encoding a replication protein, said replication protein being necessary for replication of said origin of replication.

14. (Twice Amended) The pair of vectors of claim 12 wherein the component of an LCR is a component of the β-globin LCR consisting of HS3.

15. (Once Amended) The pair of vectors of claim 12 or claim 13 wherein the [LCR, or] component [thereof] of the LCR is the β-globin LCR [or component thereof] excluding site HS2.

23. (Once Amended) A method of obtaining persistent, tissue-specific expression of a gene of interest in a host cell in culture, comprising culturing a host cell transfected with the vector of claim [1] 2 or the pair of vectors of claim [12]13.

Please cancel claim 2 without prejudice.